A I D S TREATMENT N E W S

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John S. James
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Contents

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Subscription and Editorial Office:
AIDS Treatment News
Philadelphia FIGHT
1233 Locust St., 5th floor
Philadelphia, PA 19107
800-TREAT-1-2 toll-free U.S. and Canada
fax: 215-985-4952
email: aidsnews@aidsnews.org
web: http://www.aidsnews.org

Editor and Publisher: John S. James

Statement of Purpose:

AIDS Treatment News reports on experimental and standard treatments, especially those available now. We interview physicians, scientists, other health professionals, and persons with AIDS or HIV; we also collect information from meetings and conferences, medical journals, and computer databases. Long-term survivors have usually tried many different treatments, and found combinations that work for them. *AIDS Treatment News* does not recommend particular therapies, but seeks to increase the options available.

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Reproduce.....

While exploring better ways to sell information online, we developed a design that we believe will be important in online commerce generally -- financial accounts each with its own Web control center, allowing each account to have its own settings for dozens or hundreds of options and services offered by the server, and also to reproduce children accounts without limit, through any number of generations. Each new account will inherit the options and services of its parent, and allow owners to make inherited changes if they wish -- leading to family trees of related accounts that can evolve through practical use. This article shows how organizations can let people give as much or as little as they choose, without breaking out of the moment to do all the steps usually necessary to pay money.

Campaign to End AIDS (C2EA) -- New National Mobilization

by Suzy Subways

The Campaign to End AIDS, which is planning five days of action in Washington, DC, from October 8th to 12th, has launched an ambitious grassroots effort to revive American AIDS activism by building solid networks in every state and U.S. territory. With demands for universal treatment and services, science-based HIV prevention, more research and an end to stigma, C2EA argues that the world finally has the tools to stop the epidemic – but that those in power lack the political will to make these tools available to people who need them. In the works for October are rallies, lobbying visits, a national organizing summit, a concert on the Mall, and a prayer breakfast.

Seven playfully self-titled caravans will travel to the nation's capital, including the Heart O' the Land Caravan starting in Oakland, the Nor'easter from New England, the Tropical Storm out of Miami, and Paving the Way, whose participants will be walking from New York City. Valerie Jimenez, Paving the Way coordinator, expects at least 100 to

brave the entire 21-day hike, plus as many as 1,000 at a time to join up for a day or two between cities, where marchers will demonstrate to draw attention to issues affecting local AIDS communities. Hawaii organizers will hold a PBS telethon October 1, complete with hula dancers, to raise money for airfare to LA, where they'll meet up with the Enchantment Express to drive across the country.

The campaign has directed new energy to enlist faith groups. "A Baptist church in an African-American community just outside Mobile, Alabama, will be hosting a caravan and holding a prayer service," says Charles King, C2EA co-chair and the CEO of New York City-based Housing Works. "That's just one example of the churches, which would not traditionally have been seen as a natural alliance for LGBT communities, that have strongly come on board."

In June, about a hundred young people (ages 16 to 26) converged in Denver for C2EA's Youth Action Institute to hone their skills for hometown advocacy and meet others doing the same work. "There were young people from Mississippi and Tennessee who feel so isolated in their communities, but who are very experienced organizers," says Sam Sitrin of ACT UP Philadelphia. Julie Davids, C2EA steering committee member and Nor'easter co-coordinator, urges older folks to join C2EA and become mentors. "This is an unprecedented opportunity to pass on a legacy to the next generation of the AIDS movement," she says.

To get involved, you can register online at http://www.CampaignToEndAIDS.org or call 1-877-END-AIDS. You can also contact the field organizer who is coordinating the caravan stopping in a town near you. Their names and email addresses are listed below. Click on "caravans" on the C2EA website to see the map showing their routes.

Tropical Storm (departing from Miami and stopping along the East Coast and the Eastern Shore of Maryland and Delaware): Yocasta Juliao, yocastajuliao@aol.com.

American Heritage (departing from Portland, Oregon and stopping in Boise, Des Moines and other points along the upper Midwest): Sean Barry, spbarry@gmail.com.

Northern Tier (departing from Seattle and stopping in Minneapolis, Detroit, and points far North): Sean Barry, spbarry@gmail.com.

Soul of the South (departing from Brownsville, Texas, and stopping in Louisiana, Mississippi, the Florida panhandle, and other southern locations): Larry Bryant, larrybryant_1@msn.com.

Waves (departing from San Diego and stopping in southern Arizona, New Mexico, northern Texas, Arkansas, Louisiana, Mississippi, Alabama, Tennessee, North Carolina, and Virginia): Larry Bryant, larrybryant_1@msn.com.

Heart O' the Land (departing from Oakland and stopping in Nevada, Utah, Colorado, Kansas, Missouri, southern Illinois, Indiana, Kentucky, West Virginia and Virginia): Cedric Smoots, cedricearlsmoots@sbcglobal.net.

Enchantment Express (departing from LA and stopping in Las Vegas, Flagstaff, northern New Mexico, the Texas panhandle, Oklahoma, Missouri, Arkansas, Tennessee, North Carolina and Richmond) Cedric Smoots, cedricearlsmoots@sbcglobal.net.

Paving the Way (departing by foot from New York City and stopping in New Jersey, Philadelphia, Delaware, and Maryland): Valerie Jimenez, jimenez@housingworks.org.

Nor'easter (departing from Burlington, Vermont and stopping in New Hampshire, Maine, Massachusetts, Rhode Island,

Connecticut, western New York, Pennsylvania, and Maryland): Sonny Suchdev, sonny@champnetwork.org.

Washington, DC Kaytee Riek riek@housingworks.org

Note (JSJ): See *The Economist*, July 16, 2005, "The Glue of Society" for an overview of what is happening in voluntary associations; it's in a separate "A Survey of America" section. C2EA is the kind of organizing needed -- with local groups and personal involvement, not just a national office where people send checks.

Major Treatment Conference in Rio, July 24-27

The third IAS Conference on Pathogenesis and Treatment is taking place in Rio de Janeiro, Brazil, July 24-27, 2005. This conference, organized every two years by the International AIDS Society and co-sponsored by organizations including the Brazilian national AIDS program, the ANRS (French National Agency for Research on HIV and Viral Hepatitis), the Bill and Melinda Gates Foundation, International Medical Press, and nine major pharmaceutical companies, has become important very quickly -- probably because it has a strong medical and scientific focus, and is more accessible than the Retroviruses conference in the U.S. For more information about this and related international AIDS conferences see:

http://www.ias-2005.org/ -- home page of the current conference in Rio;

http://www.iasociety.org/ -- home page of the International AIDS Society;

http://www.aids2006.org/ -- next year's big conference, the XVI International AIDS Conference (also co-sponsored by the International AIDS Society) August 13-18, 2006 in Toronto, Canada;

http://www.ias2007.org/ -- the next IAS Conference on Pathogenesis and Treatment, July 22-25, 2007 in Sydney, Australia.

We will have information about presentations in future issues. Web sites that will be reporting this conference include two that are officially IAS online partners: **http://www.kaisernetwork.org/rio2005** (Kaiser Family Foundation), and **http://www.hiv.medscape.com/** (Medscape). Also see **http://www.clinicaloptions.com/** (Clinical Care Options) and other sites.

New Publications: Announcements in *AIDS Treatment News*

by John S. James

We are trying a new section of short announcements of recent published articles and other information that our readers may want to know about.

For this first test we chose to focus on the medical journals listed at HIV InSite, at http://hivinsite.ucsf.edu/InSite?page=li-04-35. But other publications may be more useful to our readers than most journal articles. And news feeds on current research are already available. We are exploring how to be useful, and invite your input to aidsnews@aidsnews.org.

With medical journals, getting the original articles can be a problem, especially for those who are not part of a large university, hospital, corporation, or other institution that can negotiate top-of-the-line access that includes leading journals. As we learn more about legal ways for readers to get articles in some cases, we will share them. Fortunately the secondary materials that report on a range of research, and on thinking in the medical world, are usually free for everyone online; for most people these are more useful than original research reports. And the research papers almost always have a free abstract available (since otherwise the work could not be indexed effectively in large public databases, and would lose much of its audience and influence).

Recently there has been much concern about industry influence and other editorial problems of medical journals. We note three articles that address these issues at the end of this section.

* * *

Major Study of "Discordant" Response -- Viral Control but Incomplete CD4 Response

This important research from the Swiss HIV Cohort Study (1) looks at patients who responded virologically to antiretrovirals (viral load consistently under 1000 for at least five years) to find the differences between those who had an "incomplete" CD4 response (defined as not reaching a CD4 count of 500), vs. those with a "complete" response to at least 500. Older age, lower CD4 baseline, and longer HIV infection were associated with incomplete CD4 recovery. CD4 response during the first three to six months of antiretroviral treatment was a good predictor of who would respond at five years (this study looked only at those who did control viral load to under 1,000 copies).

However, this study in 293 patients did not find a statistically significant difference in number of patients who had AIDS-related events -- 14.4% of those with "complete" CD4 recovery and 21% incomplete, but this difference was not enough to reach the customary .05 level of statistical significance.

In the future, this kind of research could help doctors and patients know what to expect from current antiretroviral treatment, avoiding unnecessary drug use or regimen switches.

A 3-page editorial summary (2) published with the research report is a good place to start for understanding this study and its importance. The journal, *Clinical Infectious Diseases,* has made both papers available free to nonsubscribers online. Visit http://www.journals.uchicago.edu/CID/journal/available.html, select volume 41 number 3, and scroll down to click on the articles starting on pages 361 and 373.

References

(1) Kaufmann GR, Furrer H, Ledergerber B and others. Characteristics, determinants, and clinical relevance of CD4 T cell recovery to <500 cells/µL in HIV type 1-infected individuals receiving potent antiretroviral therapy. *Clinical Infectious Diseases*. August 1, 2005; volume 41, pages 361-372.

(2) Sasson SC, Kelleher AD, and Cooper DA. The modern ART of HIV infection management: Towards a tailored approach to maximize CD4 T cell reconstitution. [editorial commentary] *Clinical Infectious Diseases*. August 1, 2005; volume 41, pages 373-375.

Immunology Study Finds Decreased Activation Markers Related to Better Viral Control

This study measured 60 immune-system parameters over 48 weeks, in 192 antiretroviral-experienced children from 4 months to 17 years old. The results "suggest that significant decreases in the expression of activation markers and increases in the expression of naive markers in the CD8+ T cell population may be related to better virologic control in these HIV-1–infected children, who had relatively stable immune function at the initiation of HAART. At week 44 of HAART, the major immunological parameters in these HIV-1–infected children moved from baseline values to about halfway to two-thirds of the way toward the values in healthy, uninfected children." (quote from the abstract)

Comment: This is a kind of study that has been needed for a long time, to measure immune changes in patients and correlate them with virologic and/or clinical outcomes. These studies can be done in children because, for political reasons and also due to the success of preventing maternal transmission, the amount of money for AIDS research for children is disproportionate to the number of U.S. cases. Immunological studies in patients have lagged far behind antiviral studies, since there is little commercial interest in them, as there are no approved immune treatments for HIV infection. Fortunately this study could be done because one political influence on research helped to correct another.

Reference: Rosenblatt HM, Stanley KE,

Song LY and others. Immunological response to highly active antiretroviral therapy in children with clinically stable HIV-1 infection. *Journal of Infectious Diseases.* August 1, 2005; volume 192, number 3, pages 445-455.

Four Antiretrovirals Reduced to Three After 48 Weeks

A trial started over 400 antiretroviral-naive patients on an intensive 4-drug regimen -- Trizivir, (AZT, 3TC, and abacavir) together with Sustiva (efavirenz). After 48 weeks, 282 of them were randomized to either continue that regimen, or to drop the Sustiva, for another 48 weeks in the study. "After induction with ABC/3TC/ZDV + EFV, simplification to ABC/3TC/ZDV alone maintained virologic control and immunologic response, reduced fasting lipids and ART-associated adverse events, and improved adherence" (quoted from abstract).

There were more virologic failures in the group that dropped the Sustiva and switched to three drugs (16 vs. 8), but this difference did not reach statistical significance (P=0.134).

Markowitz M, Hill-Zabala C, Lang J, and others, for the ESS40013 study team. Induction With Abacavir/Lamivudine/Zidovudine Plus Efavirenz for 48 Weeks Followed by 48-Week Maintenance With Abacavir/Lamivudine/Zidovudine Alone in Antiretroviral-Naive HIV-1-Infected Patients. *JAIDS* (*Journal of Acquired Immune Deficiency Syndromes*). July 1, 3005; volume 39, number 3, pages 257-264.

UK HIV Liver Transplant Guidelines Published

Guidelines for Liver Transplantation in Patients with HIV Infection, a 12-page document developed by the British HIV Association and the UK and Ireland Liver Transplantation Centres, was published in April 2005. In the past patients with HIV were almost always excluded, but now about 200 have received liver transplants worldwide, and the UK guidelines make it clear that transplants are appropriate for many patients.

A brief summary of the guidelines was published by Aidsmap, http://www.aidsmap.com/en/news/2D0F99CE-3D40-40D3-8E5A-B66FC162AF3A.asp

The guidelines themselves are available for download at http://www.bhiva.org/guidelines/2005/liver/

HIV Protease Inhibitors vs. Malaria

Researchers at San Francisco General Hospital and the Howard Hughes Institute tested seven HIV protease inhibitors in the laboratory and found that all of them have activity against *Plasmodium falciparum* at concentrations found in patients. The best one in their tests was Kaletra. "These findings suggest that use of HIV-1 protease inhibitors may offer clinically relevant antimalarial activity."

Comment: If protease inhibitors that were never designed or optimized for malaria can be active, it should be possible to produce much better anti-malarial drugs in this class.

Reference: Parikh S, Gut J, Istvan E, Goldberg DE, Havlier DV, and Rosenthal PJ. Antimalarial activity of human immunodeficiency virus type 1 protease inhibitors. *Antimicrobial Agents and Chemotherapy.* July 2005; volume 49, number 7, pages 2983-2985.

Hepatitis C and Unsafe Sex: There Is Some Risk

By far the biggest risk of getting hepatitis C is from injecting drugs with shared needles. It has long been known that sexual transmission is much less common, but it can occur. Now some more data are available from the Swiss HIV Cohort Study.

This study recently reported that among

participants with a history of injection drug use, there were 7.4 new cases of hepatitis C per 100 patient year -- compared to 0.23 per 100 patient years for those without the drug use. Among those who did not inject drugs, those who reported unsafe sex had 0.7 per 100 patient years, while those who did not had 0.2 cases.

In other words, in this group being studied, injecting drugs was associated with 30 times the risk of getting hepatitis C. For those not injecting drugs, unsafe sex was associated with 3.5 times the risk.

Rauch A, Rickenbach M, Weber R and others, and the Swiss HIV Cohort Group. Unsafe Sex and Increased Incidence of Hepatitis C Virus Infection among HIV-Infected Men Who Have Sex with Men: The Swiss HIV Cohort Study. *Clinical Infectious Diseases.* 2005; volume 41, pages 395-402.

"Medical Journals Are an Extension of the Marketing Arm of Pharmaceutical Companies"

The article with this title, published in the May 2005 *PLoS Medicine*, is particularly interesting because the author was an editor of the *British Medical Journal* for 25 years -- and for 13 of them was editor and chief executive of the BMJ Publishing Group, responsible for the profits of the BMJ and 25 other journals. Some of his observations are different from what the public thinks.

He found that advertising was not the big problem, but "the least corrupting form of dependence. The advertisements may often be misleading and the profits worth millions, but the advertisements are there for all to see and criticise" -- and people learn to discount advertising anyway. The big problem is clinical trials -- which readers see as one of the highest forms of evidence, which have the journal's stamp of approval, and which are distributed around the world, often with global media coverage. "For a drug company, a favourable trial is worth thousands of pages of advertising," which is why companies sometimes pay more than a million dollars just to buy reprints to distribute to doctors and others. And studies have found that these published articles on trials rarely produce results unfavorable to the company that funded them. "The evidence is strong that companies are getting the results they want" -- in large part by asking the right questions, which can be done in many ways, which much of the rest of the article describes.

Why doesn't the system peer review (accepting, rejecting, or improving the articles based on reviews by scientific colleagues) catch this? The author said he "must confess that it took me almost a quarter of a century editing for the BMJ to wake up to what was happening. Editors work by considering the studies submitted to them. They ask the authors to send them any related studies, but editors have no other mechanism to know what other unpublished studies exist. It's hard even to know about related studies that are published, and it may be impossible to tell that studies are describing results from some of the same patients." Many journals very much want to publish randomly controlled trials (because they believe they are the best). And such articles are highly profitable for the journals.

To address the problem, "Firstly, we need more public funding of trials, particularly of large head-to-head trials of all the treatments available for treating a condition. Secondly, journals should perhaps stop publishing trials. Instead, the protocols and results should be made available on regulated Web sites." The journals would then publish articles critically describing them -- but the reporting of the results themselves would be less subject to manipulation.

Reference: Smith, R. Medical journals are an extension of the marketing arm of pharmaceutical companies. *PLoS Medicine.* May 2005; volume 2, issue 5: e138. All PLoS articles are freely available to anyone online; for this and other publications in *PLoS Medicine,* see http://medicine.plosjournals.org/.

Major Medical Journals Will Require That Randomized Trials Be Registered

Anyone conducting medical research on humans is already required to register most major trials in public databases, under international standards and the laws of many

countries. But this requirement has often been ignored or evaded by companies that do not want to let competitors know what they are doing. In May 2005 the *New England Journal of Medicine*, *JAMA* (*Journal of the American Medical Association*), *The Lancet*, *Annals of Internal Medicine*, and other journals, have announced that for trials that start recruiting after July 1, 2005 (or a September 13 for ongoing trials), they "will consider a trial for publication only if it has been registered before enrollment of the first patient." This applies to "any research project that prospectively assigns human subjects to intervention and comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome" -- so it would not apply to most phase I trials (which could still be registered voluntarily).

Registration must include at least the 20 fields specified by the World Health Organization (the fields are named in the May 2005 statement, referenced below). And the journals will review the contents of the fields; meaningless phrases like "investigational drug" will not be accepted for the name of the intervention being studied.

"The purpose of a clinical trials registry is to promote the public good by ensuring that everyone can find key information about every clinical trial whose principal aim is to shape medical decision-making. ... Every trial participant and every investigator should be asking, 'Is this clinical trial fully registered?'"

Reference: "Is this clinical trial fully registered?" You can find it in many medical journals and elsewhere by doing a Google or other search on the title (include the quotation marks).

Journal Will Require Clinical Trials to Summarize Earlier Results

Starting in August 2005, *The Lancet* "will require authors of clinical trials submitted to *The Lancet* to include a clear summary of previous research findings, and to explain how their trial's findings affect this summary."

In a statement published July 9, *The Lancet* explained that much of the reason for this requirement is to prevent research on patients that is unethical because it does not need to be done at all, as the superiority of one treatment tested over another was already known from previous work. "Unnecessary and badly presented clinical research injures volunteers and patients as surely as any other form of bad medicine, as well as wasting resources and abusing the trust placed in investigators by their trial participants." The statement also notes the problem of unpublished research, which is being addressed by requiring companies to register human trials (so that future researchers will not expose volunteers to unnecessary risks because they did not know that the previous studies had been done).

Comment: It is astonishing that such a rule would need to be required. Why wouldn't any report of a clinical trial summarize previous work? One practical problem may be that it takes so long for trials to be funded and organized, with all the negotiations, permissions, and hiring of staff, plus the time for recruiting volunteers, then for the trial to actually run, and then the time to prepare the data and write and publish the results, that by the end of all this it may be clear that the trial was no longer necessary -- a consequence the researchers may not want to advertise. Perhaps operations research (now widely recommended for healthcare delivery in areas where there has been no modern infrastructure in the past) could be applied to clinical trials in rich countries as well, to prevent unnecessary delays and make the research more current and relevant.

Comment on "data exclusivity": While not mentioned in *The Lancet* statement, medical ethics should also look at international trade agreements that require unnecessary trials. Under data exclusivity, a controversial rule first imposed in 1987, for a period of about eight years after approval of a new drug, a country cannot accept an application for a generic bioequivalent to a brand-name drug even if the patent is expired or is otherwise not a problem, because that is called "unfair" use of the knowledge that the brand-name drug worked in the first place. Instead, a new clinical trial would have to start over and test the generic to treat the disease in patients in order to be approved for that use, as if the first trial had not been done -- an unnecessary trial because it would require patients to take risks to re-prove what had already been well established. In addition, the re-run trial would likely expose patients to treatment known to be inferior. It is astonishing that the U.S. and other rich countries routinely impose trade rules that would require unethical trials, to invent yet another excuse to block inexpensive